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REVIEW ARTICLE

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Cutaneous metastasectomy: Is there a role in breast cancer? A systematic review and overview of current treatment modalities

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Abstract

Cutaneous metastases (CM) are neoplastic lesions involving the dermis or subcutaneous tissues, originating from another primary tumor. Breast cancer is commonest primary solid tumor, representing 24%–50% of CM patients. There is no "standard of care" on management. In particular, the role of surgery in the treatment of cutaneous metastases from breast carcinoma (CMBC) remains controversial. This systematic review evaluates the role of cutaneous metastasectomy in breast cancer and provides an overview of existing treatment types.

KEYWORDS

breast cancer, cutaneous metastases, dermal metastases, metastasectomy, surgery

1 | INTRODUCTION

Cutaneous metastases from breast carcinoma (CMBC) involve the dermis or subcutaneous tissue.[1] Breast cancer is the most common solid tumor that causes cutaneous metastases, representing 24%–50% of these patients.[2,3] CMBC is different from both locally advanced breast cancer (LABC) and inflammatory breast cancer (IBC), which have different patho-etiologies. LABC involves extension of the primary tumor into the soft tissue and skin, often presenting as a "fungating breast mass" (Figure 1). These patients are frequently in denial about their disease and usually present very late.[4] IBC is a subset of LABC that is highly angioinvasive and presents with breast erythema, edema, and/or a peau d'orange appearance (Figure 2)[5] This may occur in the absence of a palpable breast mass.[5]

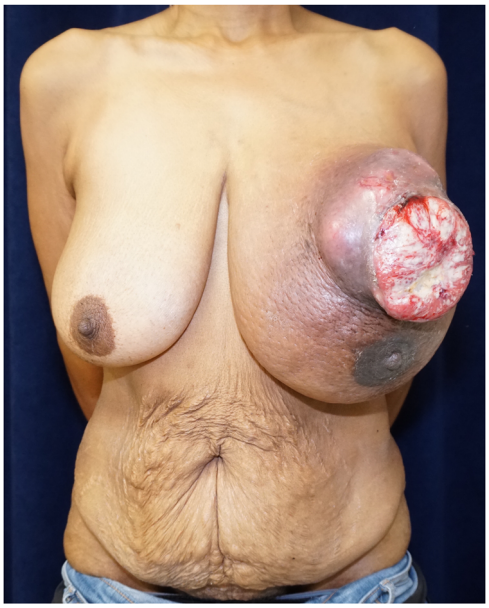

FIGURE 1 Locally advanced left breast cancer presenting with a fungating mass, due to significant delay in seeking treatment

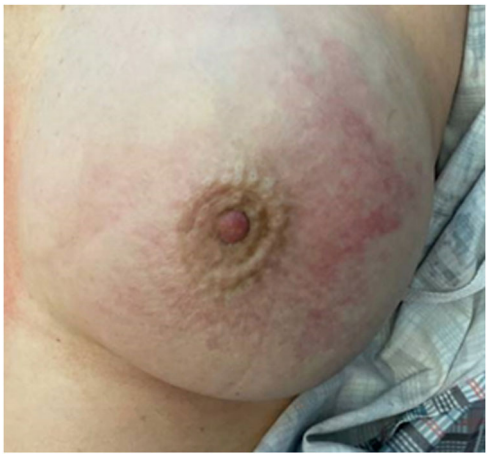

FIGURE 2 This patient shows the typical skin erythema associated with inflammatory breast cancer. There is often also a peau d'orange appearance

Presentation and diagnosis of CMBC are often delayed or missed because the clinical signs are highly variable and often look benign. These include rashes, nodules, plaques, papules, pigmented lesions, and inflammatory skin changes (Figure 3A–D).[1,6] They may present close (Figure 3C), or distant (Figure 3D), to the primary breast cancer or mastectomy site; however, they most commonly present on the chest wall (Figure 3A,C), abdomen, and scalp.[1] Less commonly, they arise on the back (Figure 3D), upper arms (Figure 3C), and lower abdomen, with rare cases occurring in the buttocks, perianal region, lower extremities, and eyelids.[1] Symptomatic lesions may present with wound drainage, pain, and bleeding (Figure 4), adversely impacting patient quality of life.[7] These skin manifestations may be related to breast cancer subtypes.[8] As reported in one study, hormone receptor-positive cancers tend to give rise to skin ulceration, triple-negative (TN) HER2 overexpressing tumors more often involve soft tissue infiltration, and TN tumors most frequently give rise to erythematous infiltration.[8] Cutaneous metastases are believed to occur via lymphatic or vascular spread, typically as a recurrence of primary cancer, as evidenced by the receptor status, or as de novo disease.[1,9]

CMBC may arise as the initial presentation of breast cancer, but is often a late-stage condition after initial breast cancer diagnosis and treatment.[10] They are associated with a poor prognosis, particularly when there are concomitant visceral metastases.[11]

Traditional teaching is that cutaneous metastases, in the setting of any primary cancer, reflects widely disseminated disease.[12] Therefore, local surgical control is considered futile, conferring little impact on overall survival.[12] Following biopsy-confirmed diagnoses of CMBC, conventional practice, though not evidenced-based, is to begin systemic therapy. Local treatments are focused on palliation of symptoms, such as wound care and hemostasis. Surgical excision, or "cutaneous metastasectomy" is generally avoided.[12]

The concept of complete metastasectomy is established in other cancers, most notably Stage 4 malignant melanoma.[13] Melanoma is the commonest primary cancer leading to cutaneous metastases.[14] Historically, surgical excision of metastases was employed due to the lack of effective drugs in melanoma. At that time, multicenter trials involving surgical excision of metastases demonstrated favorable outcomes.[15] Since then, several new drug classes (such as BRAF and MEK pathway inhibitors) have resulted in dramatic improvements in survival outcomes.[16] Despite this, there is emerging data showing a synergist effect of combining surgical excision and systemic therapy.[16] A recent retrospective matched-pair analysis found that surgical resection combined with systemic therapy, either upfront surgery followed by systemic therapy or neoadjuvant chemotherapy followed by surgery, conferred a survival benefit over systemic therapy alone (27 vs. 11.5 months median melanoma survival [MMS]).[15]

In CMBC, it remains to be established whether surgical resection provides any survival benefit. Furthermore, there are a large variety of nonsurgical treatment options (local and systemic), currently in use, but no comparative data is available. It is also unknown which treatments are more effective. More importantly, it remains to be determined whether any local treatment can both palliate symptoms and provide "cytoreduction," potentially leading to increased survival or even curative treatment.[17] This review primarily aims to address the role of surgical excision in CMBC. We also introduce and summarize the current literature on nonsurgical treatment modalities used for cutaneous metastatic lesions in primary breast cancer.

2 | METHODS

This study was performed in accordance with preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines for designing and implementing systematic review studies.[18]

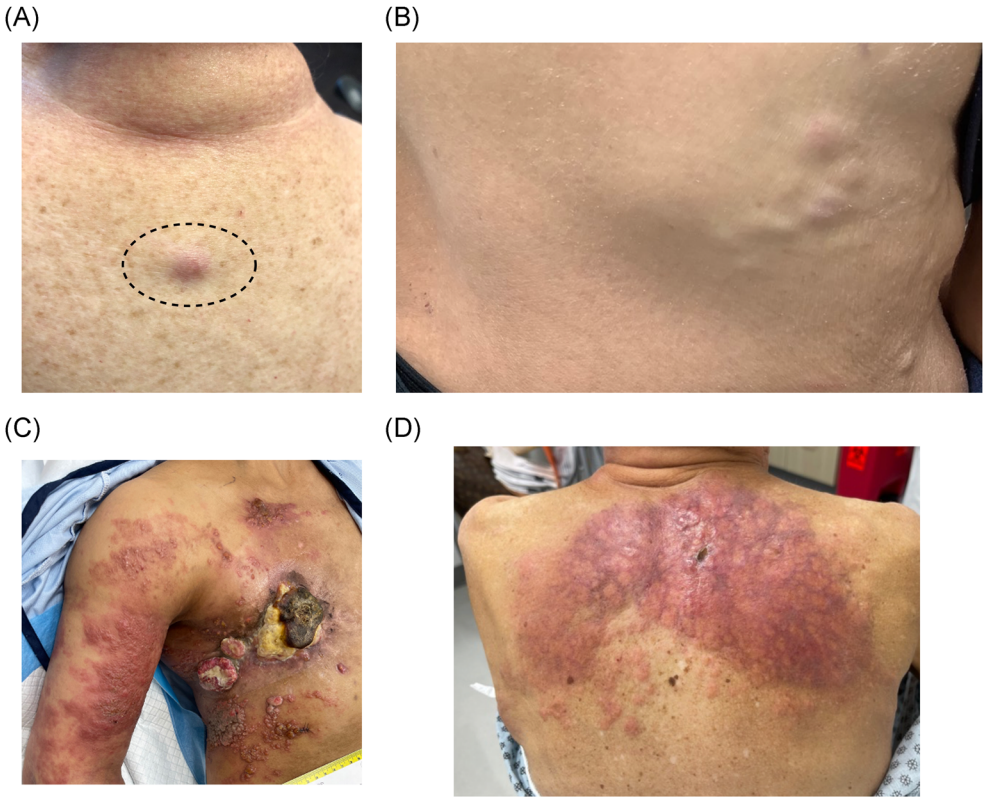

FIGURE 3 (A) This shows a single nodule cutaneous metastases on the upper anterior chest 2 years after patient had unilateral lumpectomy and radiation. The proposed elliptical excision in the dashed black line, with wide margins, can be closed after some undermining of tissues. (B) This patient presented with subcutaneous nodules on the posterior lower trunk that could have been mistaken for mosquito bites. This area is quite extensive and would not be easily amenable to closure. (C) This patient had cutaneous metastases presenting with numerous indurated papules and plaques with ulcerated nodules over the right chest wall and right upper extremity. This is too extensive for surgical excision. (D) This breast cancer patient presented with cutaneous metastases in the form of a large indurated nodular plaque on the back. This is too extensive for surgical excision

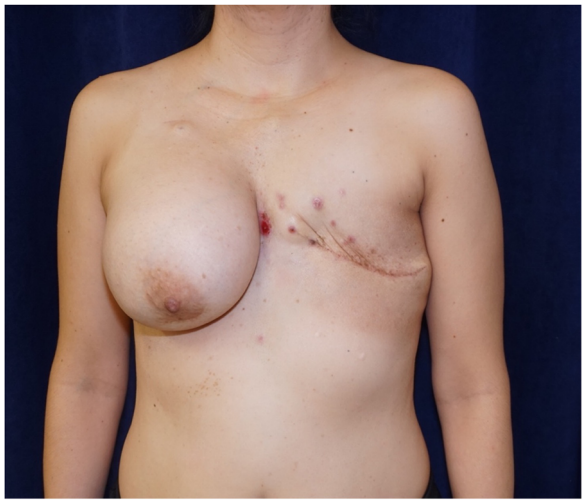

FIGURE 4 This patient had multiple cutaneous metastases presenting as nodules after left mastectomy. Some of these were bleeding, which prompted her to seek medical attention. She did have visceral metastases and deemed not a surgical candidate. We managed this with coagulation using topical silver nitrate

2.1 | Eligibility criteria

The search was restricted to articles in English, published between January 1980 and January 2022, and reporting on human subjects or animal models. Given the limited data in the literature, clinical trials, randomized control trials, case reports, and case series were included. The final search was completed on January 2, 2022.

A systematic literature search was conducted using SCOPUS and MEDLINE (OVID), as well as by manually checking the reference lists of retrieved articles and reviews, once relevance was determined.

2.2 | Search query

Search terms used include: "(cutaneous metastasis OR dermal metastasis) AND (breast cancer OR breast neoplasm*)," "(dermal neoplasm OR cutaneous neoplasm) AND (breast cancer OR breast neoplasm*)," and "(cutaneous metastasis OR dermal metastasis) AND (breast cancer OR breast neoplasm*) AND (DNA OR epigenomic OR genomic OR proteomic OR sequence OR precision)."

2.3 | Study selection

The titles, abstracts, and full texts were reviewed independently by two readers (Samantha Huang and Wai-Yee Li) to determine eligibility. In all instances, differences in opinion were resolved by discussion. Articles were included if they reported on cutaneous metastases arising from primary cancer of the breast. Articles that discussed non-cutaneous metastases, non-breast primary cancers, or inflammatory breast cancer, as well as those that did not discuss treatment, were excluded.

2.4 | Risk of bias

To assess for study bias, we assigned a level of evidence for each study, based on the quality of study design and statistical validity.[19]

2.5 | Data items/summary measures

Data obtained included year of publication, study design, study objectives, patient age, time to presentation, modality used to treat cutaneous metastases, response rate, and survival time.

3 | RESULTS

The database search from SCOPUS and MEDLINE (OVID) yielded 3219 unique titles. After screening titles and abstracts for eligibility, 110 articles were identified for review (Figure 5). A total of 1392 CMBC patients were represented in these studies. There were 12 publications, involving 50 patients, that were focused on surgical management of CMBC. Reports on chemotherapy studies were most common, with 51 publications. This was followed by electrochemotherapy (ECT) with 16 publications; radiation with 15 publications; aromatase inhibitors with 13 articles and topical therapy with 10 studies. The other treatment modalities had less publications; Photodynamic therapy (PDT; n = number of publications = 9); targeted therapy (n = 9), immunomodulators (n = 3), and novel agents (n = 2). An overview of these studies is summarized in Table 1. A description of each treatment modality is outlined in Table 2. Study characteristics, response rates, and outcomes are outlined in Table 3 (all studies reporting on surgery) and Table 4 (selected studies reporting on chemotherapy), and Table 5 (summary of selected study outcomes from remaining nonsurgical treatment modalities).

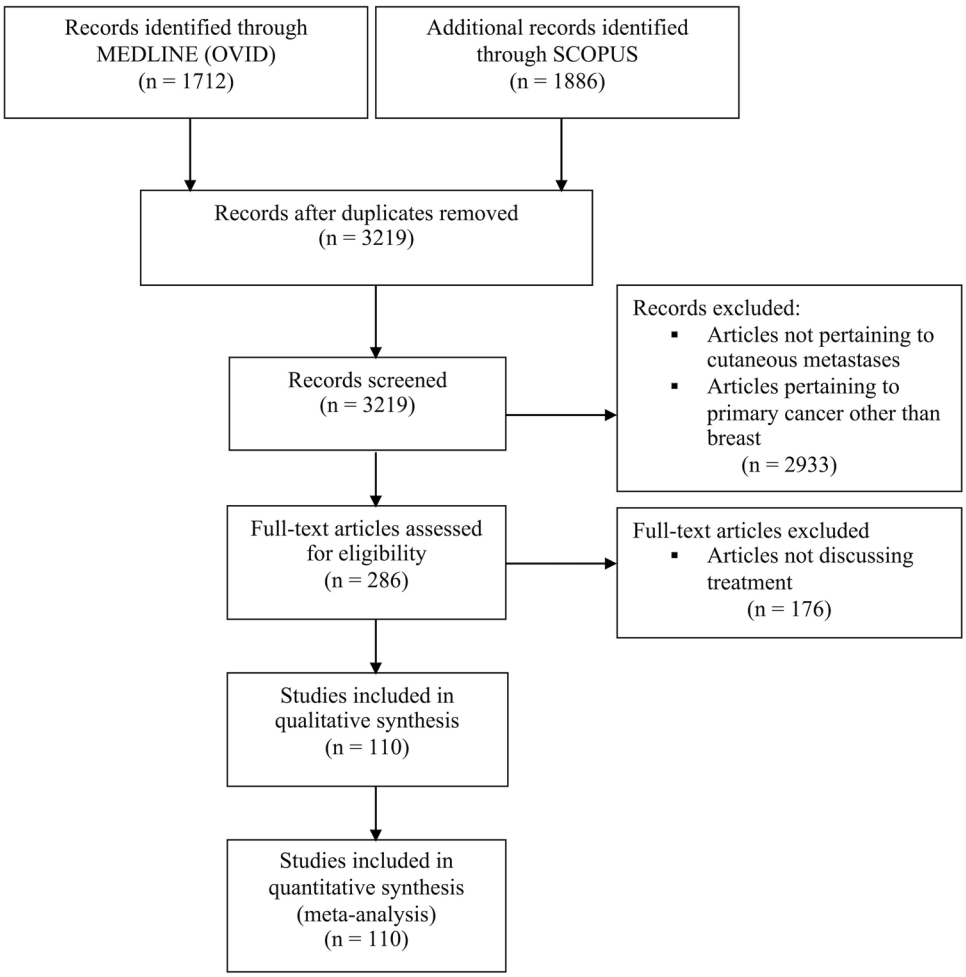

FIGURE 5 PRISMA flow diagram of articles retrieved and assessed for eligibility

TABLE 1 Summary of included studies

Treatment modality	Number of studies	Patients (*n*)	Longest follow-up period for surviving patients (years)
Chemotherapy	51	305	18
Electrochemotherapy	16	440	1
Surgery	12	50	8
Radiotherapy	15	113	4
Aromatase inhibitors	13	14	9.7
Topical therapy	10	155	0.5
Photodynamic therapy	9	102	1
Targeted therapy	9	79	3.8[a]
Immunomodulators	3	39	–
Other novel agents	2	19	–
	Total number patients	1674	
	Breast cancer specific	1392	

[a]With Bevacizumab.

4 | SURGICAL MANAGEMENT IN CMBC

Surgery was reported as both a first-line and salvage treatment for CMBC, in the form of mastectomies and local excision. Of the 12 publications reporting on surgical management (Table 3), only three reports involved surgery alone. Nine studies involved a combination of surgery and chemotherapy, and two of these also included radiation after chemotherapy and surgery. Patients with solitary lesions were more likely to be treated surgically than those with multiple cutaneous lesions.[20] Single lesions represent lower disease burden, and therefore were more amenable to primary closure with the avoidance of complex reconstruction. They were also considered to be less refractory to recurrence after complete excision.[17] Lesions in skin that were poorly vascularized, or had prior radiation or surgery, were less likely to be surgically removed due to concerns of impaired postoperative healing.[17,20–24] Patients with delayed presentation and distant metastases were generally poor surgical candidates, and usually less aggressive palliative therapy was chosen.[25,26]

The outcomes of surgical excision following primary breast cancer treatment are limited to a few case reports and case series. Two case reports by Santiago et al.[27] and Varricchio et al.[20] described two patients who underwent mastectomies followed by myocutaneous flap reconstruction and adjuvant chemotherapy. These patients remained disease-free up to 17 months after surgery.[20,27] In a case series by Salvadori et al.,[28] local control was reported in 32 out of 39 patients who underwent tumor excision and adjuvant chemotherapy. Of these patients, 21 remained alive and disease-free throughout the median follow-up time of 48 months.[28]

Additionally, two case reports discussed surgical excision of cutaneous metastases arising in areas distant from the primary breast cancer site. In one case report by Alizadeh et al.,[29] the patient had a cutaneous recurrence to the scalp. She was treated with preoperative chemotherapy followed by metastasectomy, skin graft, and radiation. The patient was disease-free during the study's 3-year follow-up period.[29] In another case report by Lam et al.,[30] the patient underwent Mohs surgery for cutaneous metastases to the eyelid and was found to have no local recurrence despite developing systemic metastases in the following 3 years.[30]

5 | NONSURGICAL THERAPIES IN CMBC

5.1 | Photodynamic therapy

PDT is a noninvasive light therapy applied to tissues that have been pretreated with a photosensitizing agent, known as the "photosensitizer."[12] The light activates the photosensitizing agent, which stimulates reactive oxygen species, causing selective tumor cell death.[12,31–33] The choice of light is dependent on the lesion and photosensitizer used. Blue light, in the 400 nm range, is better suited for superficial cutaneous lesions; while, red light (600 nm range) is used for larger, bulkier tumors, requiring deeper penetration.[34]

PDT was described in nine studies, representing 102 patients from small prospective cohort studies and one clinical trial. The complete response rate ranged from 11.1%[35] to 92%[36] and the partial response rate ranged from 8%[12,36] to 55.6%[35] over a 6- to 12-month follow-up period.

Investigative studies have been performed using various pretreatment strategies and photosensitizers in an effort to improve outcomes and minimize side effects. Pretreatment with systemic vitamin D has been shown to increase tumor cell death in mouse models undergoing PDT treatment with 5-aminolevulinate (ALA).[32]

TABLE 2 Overview of treatment modalities

Category	Agent(s)	Mechanism of action	Indication	Treatment procedure	Advantages	Disadvantages/side effects
Surgery	–	Excision	Small lesions Surgical candidateOdorous, bleeding, draining lesions	Wide local Excisioncompletion mastectomy primary closure Mohs surgery	Potentially cures	May require further surgery for recurrence or after incomplete excision
PDT	*Photosensitizers*: Hematoporphyrin ALA TPPSa	Laser therapy with photosensitizing agents that create reactive oxygen species leading to tumor cell death	Palliation for smaller lesions Patients who cannot tolerate aggressive therapy or surgery	1. Administer photosensitizer (intravenously, intratumorally, or topically) 2. Patients return home for 24–72 h to allow photosensitizers to accumulate in tumor tissue 3. Patients return to clinic for laser therapy	1. Can be repeated as an outpatient procedure 2. Results seen as fast as within 1 week of first treatment	Sensitivity to skin damage 4–6 weeks after treatment Pain, ecchymosis, and bleeding
Topical therapy	Imiquimod	Immunomodulator; induces apoptosis and inhibits tumor cell growth	Palliation Patients who cannot tolerate or have failed aggressive therapy	5% solution applied topically to cutaneous lesions	Noninvasive, applicable at home	Recurrence after treatment Pruritus, burning sensation, soreness, and crusting
	Oxygen Flow-Assisted Topical Administration of Methotrexate 5% (OFAMTX)	Increased permeability of epidermis to topical chemotherapy	Patients who cannot tolerate or have failed aggressive therapy	5% Topical methotrexate administered with Dermadrop® device (MEDDROP GMBH)	Noninvasive	Transient post-inflammatory pigmentation
	Topical 5-fluorouracil (5-FU) with Cryotherapy	Cryotherapy induced release of local inflammatory markers activates 5-FU	Patients who cannot tolerate or have failed aggressive therapy	Topical 5-FU two times daily, followed by cryotherapy every 2 weeks	Noninvasive	–
	Miltefosine	Induces apoptosis in tumor cells	Palliation Patients who cannot tolerate or have failed aggressive therapy	6% solution applied topically to cutaneous lesions two times daily	Noninvasive, applicable at home	Pruritus, erythema, and pain
	Ceramides	Induces apoptosis in tumor cells	Palliation	1% solution applied topically to cutaneous lesions two times daily	Noninvasive	Not shown to be effective

TABLE 2 (Continued)

Category	Agent(s)	Mechanism of action	Indication	Treatment procedure	Advantages	Disadvantages/side effects
			Patients who cannot tolerate or have failed aggressive therapy			
	Arsenic (AS_2O_3)	Induces apoptosis in tumor cells	Palliation Patients who cannot tolerate or have failed aggressive therapy	0.05% AS_2O_3 gel applied topically to cutaneous lesions before radiation therapy	Noninvasive, applicable at home	–
Radiotherapy	–	–	Palliation	Used in multimodal therapy, primarily with chemotherapy	Noninvasive	Need dose adjustment if prior radiated area
			Does not cure	Palliative regimen: 30 Gy in 10 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction	Widely available	
Chemotherapy	Vinorelbine Trastuzumab Capecitabine Lapatinib Eribulin 5-fluorouracil Liposomal doxorubicin	Systemic targeting of tumor cells	First line in progressive disease and/or with evidence of visceral metastases	Monotherapy or multimodal therapy	Noninvasive	Systemic cytotoxicity
			Patients with prior radiation or surgery		Widely available	
Aromatase inhibitor	Anastrozole Letrozole	Hormone based therapy	First-line or maintenance therapy	–	Oral treatment	–
Immunomodulators	LCL-LK Intralesional dendritic cell therapy	Immune cell recruitment	–	Intralesional injection	–	–
	nIFN-α with nIFN-y	Immune cell recruitment	–	Intralesional injection	–	Fever, chills, myalgias, mild, and leukopenia
ECT	Bleomycin *(most common)* Cisplatin Calcium	Electrical pulses with administration of chemotherapy agents	Palliation Patients who cannot tolerate aggressive therapy	Per ESOPE: 1. General or local anesthesia 2. Inject chemotherapeutic agent 3. Apply electrical pulses with electroporation device	1. Increased penetration of chemotherapeutic agents 2. Decreased systemic cytotoxicity of chemotherapeutic agents 3. Can be repeated as an outpatient procedure	Skin ulcers, urticaria, hypo or hyperpigmentation, and muscle aches

(Continues)

TABLE 2 (Continued)

Category	Agent(s)	Mechanism of action	Indication	Treatment procedure	Advantages	Disadvantages/side effects
Targeted therapy	Bevacizumab	Anti-VEGF factor	Used as adjunct with chemotherapy	–	–	Skin necrosis and impaired wound healing[a]
	Sunitinib	Receptor tyrosine kinase inhibitor	–	37.5 mg daily oral dose	–	–
	Pembrolizumab	Antibody targeted against PD-1 ligand (PD-L1) expressed in solid tumor cells	–	–	–	–
	Class I PI3K inhibitor CH51327799		–	Oral medication	–	–
CAR-T therapy	c-Met	Target hepatocyte growth factor receptor expressed in breast cancer cells	–	Intratumoral injection	–	Experimental Not widely available
Oncolytic viral therapy	HF10	Class I PI3K inhibitor CH51327799	–	Intratumoral injection	–	Experimental Not widely available
Other novel agents	Recombinant antibody toxin scFv (FRP5)-ETA	Recombinant antibody toxin against ErbB receptors overexpressed in tumor cells	–	–	–	–
	Topical calcitriol	Vitamin D based therapy used to inhibit cellular proliferation *(in vitro studies only)*	–	Topical application	–	–

Abbreviations: ALA, aminolevulinic acid; IFN, interferon; LCL-LK, lymphoid cell lymphokine; PI3K, intracellular phosphatidylinositol-3-kinase; TPPSa, meso-tetra-(para-sulphophenyl)-porphin.

[a]Stop bevacizumab therapy at least 5 weeks before surgery due to adverse skin effects.

TABLE 3 Summary of studies involving surgery

Author	Year published	Study type	Treatment modalities used	Patients (*n*)	Patient age (years)	Time to presentation	Time from primary cancer to CMBC diagnosis	Longest follow-up period	Response rate	Response rate (*n*)	Survived	LOE
Alizedah	2018	C	Surgery, Chemotherapy, Radiotherapy	1	44	12 mo	0	3 yr	–	–	Y	VI
Chandanwale	2011	C	Surgery, Chemotherapy	1	60	–	–	–	–	–	–	VI
Goodier	2010	C	Surgery, Chemotherapy	1	68	–	–	–			–	VI
Lam	2013	C	Surgery (Mohs)	1	59	–	4 yr	3 yr			Y	VI
Muller	2011	C	Surgery, Chemotherapy, Bevacizumab	1	61	4 mo	–	2 mo	–	–	N[a]	VI
Poovaneswaran	2013	C	Surgery, Chemotherapy	1	45	–	1 yr	6 mo	–	–	Y	VI
Salvadori	1992	C	Surgery	39	–	–	–	48 mo (median)	–	–	–	IV
Santiago	2009	C	Surgery, Chemotherapy, Aromatase inhibitor, Radiotherapy	1	50	5 mo	–	24 mo	–	–	Y	VI
Sexton	1996	C	Surgery, Chemotherapy	1	66	–	3 yr	>10 mo		–	N	VI
Swapp	2012	C	Surgery, Chemotherapy	1	58	–	8 yr	2 yr		–	Y	VI
Tianco	1990	C	Surgery	1	–	–	–	35 mo	–	–	–	VI
Varricchio	2013	C	Surgery, Chemotherapy	1	59	–	2 yr	–			Y	VI

Note: C, case report or case series.

[a]Died from reason other than cutaneous metastases.

TABLE 4 Selected studies using chemotherapy

Author	Year published	Study type	Treatment modalities used	Specific chemotherapy agent studied	Number of patients (*n*)	Patient age (years)	Time to presentation	Time from primary cancer to CM diagnosis	Longest follow-up period	Survived	LO-E	Response rate	Response rate (*n*)
Alizedah	2018	C	Surgery, Chemotherapy, Radiotherapy	–	1	44	12 mo	0	3 yr	Y	VI	–	–
Arends	2001	C	Chemotherapy	–	1	50	–	–	3 yr	N	VI	–	–
Chisti	2013	C	Chemotherapy, Radiotherapy, Aromatase Inhibitors, Miltefosine	–	1	69	–	5 mo, 9 mo	26 mo	N	VI	–	–
Franchina	2012	C	Chemotherapy	Pegylated liposomal doxorubicin	2	48, 40	–	4 yr	19 mo, 31 mo	N	VI	–	–
La Verde	2013	O	Chemotherapy	Eribulin	23	57 (median)	–	–	–	–	IV	CR: 26% PR: 39% SD: 39% PD: 13%	*n* = 23 patients
Noguchi	2011	C	Chemotherapy	Trastuzumab, lapatinib	1	72	–	–	34 mo	Y	VI	–	–
Ozet	2003	C	Chemotherapy, Radiotherapy, Aromatase Inhibitors	–	1	63	10 yr	–	4 yr	Y	VI	–	–
Pizutti	2013	C	Chemotherapy	Lapatinib, capecitabine	1	61	–	–	18 yrs	Y	VI	–	–
Santiago	2009	C	Surgery, Chemotherapy, Aromatase inhibitor, Radiotherapy	–	1	50	5 mo	–	24 mo	Y	VI	–	–
Stephens	1990	R	Surgery, Chemotherapy	–	22	–	–	5 yr	5 yr	Y	IV	–	–
Swapp	2012	C	Surgery, Chemotherapy	–	1	58	–	8 yr	2 yr	Y	VI		–
Wu	2009	C	Chemotherapy, Radiotherapy	–	1	74	2 mo	0	2 yr	Y	VI	–	–

Note: C, case report or case series; CT, clinical trial; R, retrospective cohort study.

TABLE 5 Selected study outcomes from nonsurgical treatment modalities

Modality	Author	Year published	Study type	Treatment modalities used	Number of patients (*n*)	Patient age (years)	Time to presentation	Time from primary cancer to CM diagnosis	Longest follow-up period	Survived	LOE	Response rate	Response rate (*n*)
ECT	Falk	2018	RCT	ECT	6	–	–	–	12 mo	Y	III	CR: 68% PR: 15%	*n* = 19 lesions
ECT	Matthiessen	2018	CT	ECT	119	65 (median)	–	–	2 mo	–	III	CR: 50% PR: 21% SD: 18% PD: 8% Not evaluable: 3%	*n* = 90 patients
Topical Therapy	Clive	1999	CT	Miltefosine	25	54 (median)	–	–	18 wks	–	III	CR: 4% PR: 8% Minor response: 24% SD: 44% PD: 20%	*n* = 25 patients
Topical Therapy	Leonard	2001	RCT	Miltefosine	51	68 (mean)	–	–	60 days	–	II	CR: 8.3% PR: 25% SD: 7% PD: 16.7%	*n* = 24 patients
Topical Therapy	Salazar	2017	CT	Imiquimod	15	54 (mean)	–	–	–	–		CR: 36% PR: 72%	*n* = 14 patients
Radiotherapy	Alizedah	2018	C	Surgery, Chemotherapy, Radiotherapy	1	44	12 mo	0	3 yr	Y	VI	–	–
Radiotherapy	Lai	2003	CT	As2O3 Gel, Radiotherapy	7		–	–	–	–	III	CR: 42.9% PR: 42.9% SD: 14.3%	*n* = 7 patients
Aromatase Inhibitors	Damaskos	2016	C	Chemotherapy, Aromatase inhibitors	1	75	3 mo	0	5 yr	–	VI	–	–

(Continues)

TABLE 5 (Continued)

Modality	Author	Year published	Study type	Treatment modalities used	Number of patients (*n*)	Patient age (years)	Time to presentation	Time from primary cancer to CM diagnosis	Longest follow-up period	Survived	LOE	Response rate	Response rate (*n*)
Aromatase Inhibitors	Ozet	2003	C	Chemotherapy, Radiotherapy, Aromatase Inhibitors	1	63	10 yr	–	4 yr	Y	VI	–	–
PDT	Allison	2001	P	PDT	9	–	–	–	6 mo	Y	VI	CR: 89% PR: 8% NR: 3%	*n* = 102 lesions
PDT	Lapes	1996	P	PDT	9	62.6 (median)	–	–	12 mo	–	III	CR: 33.3% PR: 22.2% NR: 22.2%	*n* = 7 patients
Targeted Therapy	Blagden	2014	CT	Class I PI3K inhibitor CH51327799	38	–	–	–	–	–	III	–	–
Targeted Therapy	Gui	2018	C	Bevacizumab	1	48	–	0	46 mo	Y	VI	–	–
Targeted Therapy	Kimata	2006	CT	HF10	6	64.2	–	–	–	–	III	–	–
Targeted Therapy	Tchou	2017	CT	c-Met CAR T cells	–	–	–	–	–	–	III	–	–
Targeted Therapy	Yardley	2012	CT	Sunitinib	19	–	–	–	–	–	III	OR: 20%	*n* = 15 patients
Targeted Therapy	Yuan	2017	C	Pembrolizumab	1	69	–	<1 yr	4 mo	Y	VI	–	–

Abbreviations: C, case report; CR, complete response; CT, clinical trial; ECT, electrochemotherapy; NR, no response; OR, odds ratio; P, prospective cohort study; PD, progressive disease; PR, partial response; SD, stable disease.

Meso-tetra-(para-sulphophenyl)-porphin ($TPPS_4$) administered intravenously or intratumorally has been suggested to have a lower side effect profile than the prototypical photosensitizer hematoporphyrin; however, studies investigating $TPPS_4$ are limited.[37]

PDT tends to demonstrate palliative improvement in small lesions in the earlier stage of progression; however, it is less effective in large, bulky, and highly symptomatic tumors.[31] Its main side effect is pain and requires posttreatment wound care, making it less suitable for patients with extensive cutaneous metastases.

5.2 | Topical therapies

Topical therapies provide a noninvasive, accessible treatment that patients can apply at home. This is especially beneficial for remote and telehealth visits, as at the time of writing, we are experiencing a global COVID-19 pandemic. Topical therapy has been demonstrated to be effective as an adjuvant therapy and palliative measure in refractory disease. Notably, it may alleviate symptoms for patients who cannot tolerate the risks of surgery or more aggressive systemic therapy.

5.2.1 | Imiquimod

Imiquimod is an immunomodulator belonging to the imidazoquinoline family, known for its use in dermatological diseases.[38] It functions by stimulating both innate and adaptive immunity, through the induction of toll-like receptors (TLRs), cytokines, and apoptosis.[39]

Recently, it has been used for cutaneous metastases, typically administered as a 5% topical solution.[7,40] An in vivo study using mouse models,[40] found imiquimod to significantly inhibit tumor growth, when compared to placebos. However, the effect was temporary, as all subjects recurred within 65 days of the final imiquimod dose.[40] Additionally, they found synergistic effects by pretreating mice with radiotherapy and cyclophosphamide, suggesting a multimodal approach in delaying metastatic progression.[40] In a clinical study by Salazar et al.[41] conducted on 14 human subjects, a complete response to imiquimod therapy was achieved in 36% ($n = 5$) of patients and partial response in another 36% ($n = 5$). Responses were maintained for 4–25 and 4–28 weeks, respectively.[41] The remaining patients had stable disease (21%, $n = 3$) or progressive disease (7%, $n = 1$).[41] A case report by Henriques et al.[7] described a rapid response to imiquimod in a patient whose cutaneous metastases were poorly controlled by chemotherapy. This patient was found to have regression of her skin lesions within 1 week of starting imiquimod and an overall decrease in pain, which allowed her to discontinue oxycodone therapy.[7]

5.2.2 | Oxygen flow-assisted topical administration of methotrexate 5%

Oxygen flow-assisted topical administration of methotrexate 5% (OFAMTX5%) uses oxygen to increase the permeability of the epidermis, allowing greater penetration of topical agents.[42] A recent case report by Jouret et al.,[42] used OFAMTX5% on a CMBC patient who had failed treatment with systemic chemotherapy. In this procedure, OFAMTX5% was administered using a Dermadrop device (MEDDROP GMBH), which delivers oxygen flow simultaneously with methotrexate, using a needle. After 2 months of OFAMTX5%, the patient was in complete remission and remained disease-free during the study's 6-month follow-up period.[42]

5.2.3 | Topical 5-fluorouracil with cryotherapy

Topical 5-fluorouracil (5-FU) was reported in one case series by Krishnasamy et al.[43] In this series, two patients were treated with topical 5-FU cream twice a day, in combination with cryotherapy every 2 weeks, while still receiving chemotherapy and radiotherapy. The proposed mechanism was a synergistic effect of 5-FU with cryotherapy; whereby 5-FU's antitumor activity was induced by the release of tumor antigens and local inflammatory markers.[43] The patients reported palliation of cutaneous symptoms within 1 week to 4 months of treatment.[43] One patient saw cytoreduction at the 6-month follow-up period, while the second had complete resolution of her lesions within 19 months of treatment.[43]

5.2.4 | Miltefosine

Miltefosine is a topical cytostatic agent that has been shown to be effective in cutaneous metastases from breast cancer and cutaneous T-cell lymphoma.[22] It is an alkyl-phosphocholine that targets the cell membrane and inhibits protein kinase C, thereby halting cell differentiation.[22,44,45] In clinical trials, it has been used as a 6% solution, applied to the skin one to two times daily.[3,44,45] Response rates ranged from 33% to 36% and median treatment times varied from 10 to 14 weeks.[22,44,45] A multicenter Phase III trial performed by Leonard et al.[45] found miltefosine had a significantly higher tumor response rate when compared with placebos (33.3% vs. 4% complete response rate, $p = 0.009$). A Phase II clinical trial performed by Terwogt et al.,[44] found lesions less than 2 cm in diameter, or with lymphangiectic infiltration, to be more responsive to therapy.

As an effector of miltefosine-induced apoptosis, topical ceramides were investigated in one prospective study as a topical treatment.[46] In this study by Jatoi et al.,[46] 1% ceramide cream was applied to the skin twice a day in 13 patients. No significant tumor response was found.[46]

5.3 | Radiotherapy

Radiotherapy is another treatment option for CMBC that is widely used and available.[1] Ionizing radiation is delivered to the metastases, generating free radicals that kill tumor cells by DNA damage. It is a noninvasive method that can quickly palliate symptoms of cutaneous

metastases, such as pain or bleeding from ulceration. However, it is less effective in tumor debulking and is not curative.[1] Data specific to CMBC are limited to case reports or small case series, but demonstrate favorable outcomes.[44,45] Notably, radiation therapy is well established in the care of primary cutaneous malignancies including both melanoma and non-melanoma cancer.[46,47]

In choosing a radiotherapy regimen, considerations regarding the prior history of radiation to the skin should be considered, particularly in breast cancer patients. A repeat course of irradiation in the same area is associated with increased risk of serious toxicity, such as skin ulceration or poor wound healing, and care must be taken to reduce radiation doses appropriately.[19]

With regard to dose and technique, radiation therapy for CMBC is usually given using palliative fractionation schemes. For instance, a course of 30 Gy in 10 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction, using either photons or electrons.[48] For extensive or bulky metastases or recurrence in the chest wall, a higher dose of up to 50 Gy in 25 fractions, is also an option.[48] Case series have reported improved outcomes when combining radiation therapy with systemic therapy, such as radio-sensitizing agent 5-FU[37,49] or hyperthermia.[50] Additionally, topical arsenic (AS_2O_3) has been studied in one pilot study, as a pretreatment adjuvant to radiotherapy in CMBC.[51]

More than two decades ago, pulsed brachytherapy, used with a flexible reusable skin mold, was reported. One study of 46 patients achieved local control in 89% of patients with a median follow-up of 16 months.[47] This technique has since fallen out of favor and is not in regular use. A recent case report did report complete response in cutaneous metastases from renal cell carcinoma for 7 months (when patient died from primary disease).[48] Adjuvant radiation has been reported to be successful after surgical excision but there were no reports of neoadjuvant radiation before surgery.[48]

5.4 | Chemotherapy

Systemic chemotherapy is often the first-line treatment for patients with progressive disease and evidence of visceral metastases.[49] No specific chemotherapy regimen specific to CMBC has been reported, with evidence limited to case reports or case series. These studies report starting specific agents based on the extent of disease, biological tumor markers, and previous breast cancer treatment history.[50]

Anti-HER2 agents were the most consistently studied chemotherapy agents for CMBC, used specifically for HER2 + breast cancer patients. Of the 18 studies reporting on hormone status for CMBC patients treated with chemotherapy, 15 reported on HER2 + patients. In a case report by Giarratano et al.,[51] two patients saw complete regression of their HER2 + skin lesions following the initiation of ado-trastuzumab emtansine (TDM-1) up to the 87 and 135 weeks follow-up time points. Kamaraju et al.[52] reported on a HER2 + CMBC patient whose cutaneous metastases were initially treated with pertuzumab, docetaxel, and trastuzumab. After 2 years of recurring cutaneous metastases, she was started on nab-paclitaxel and trastuzumab, which led to the complete resolution of her skin lesions.[52] Noguchi et al.[53] reported on a patient whose HER2 + cutaneous metastases resolved after switching from trastuzumab to lapatinib and remained lesion free by the end of the study's 34-month follow-up period. Pizzuti et al.[54] also found complete resolution of HER2 + CMBC, 2 months following the initiation of lapatinib combined with capecitabine. The patient remained lesion-free for the subsequent 22 months.

Eribulin was studied in one observational study, which cited the drug's demonstrated safety in Phases II and III clinical trials for locally advanced and metastatic breast cancer.[50] In this multicenter observational study involving 23 patients with a majority HR + HER2- CMBC, eribulin led to a 26% complete response and 22% partial response rate. The remaining patients were either stable (39%) or experienced disease progression (13%).[50] The median progression-free survival time was 4.3 months.[50] The authors noted improvement in ulceration, infiltration, smell, bleeding, and pain throughout the duration of eribulin treatment.[50]

Pegylated liposomal doxorubicin (PLD) with gemcitabine has been shown to be effective in Phase II trials for triple-negative breast cancer (TNBC), with evidence for CMBC limited to one case report by Franchina et al.[55] In this study, complete regression and rapid improvement of cutaneous TNBC metastases was noted after four cycles of PLD in both patients.[55] CMBC recurred after 12 months in one patient, who was then re-started on PLD and gemcitabine. However, due to poor compliance, treatment was stopped and the patient's cutaneous metastases progressed along with additional visceral metastases.[55]

5.5 | Aromatase inhibitors

These are a type of oral hormone therapy used to decrease estrogen in the body, in postmenopausal women. The use of aromatase inhibitors in CMBC has been reported in thirteen case reports, noted to be particularly effective in ER + disease.[56] The most commonly cited drugs were anastrozole and letrozole, which can be administered with Vitamin D or calcium supplementation, to prevent the known osteoporotic side effects.[56] In six studies, anastrozole was used as the first-line therapy after the onset of cutaneous metastases, typically as a 1-mg daily dose.[56–60] Alternatively, aromatase inhibitors have been used as maintenance therapy following disease control by traditional modalities such as chemotherapy, radiotherapy, and surgery. This method was reported in three case reports, which found all three patients to have partial or complete regression of their skin lesions.[27,61,62] All patients were alive by the end of each study's follow-up period, which ranged from 2 to 5 years.[27,61,62]

5.6 | Immunomodulators/experimental

Immunotherapy involves the recruitment of immune cells to activate tumor cell death. Apart from topical imiquimod therapy described

above, multiple types of immunotherapy have been investigated as experimental therapies.

5.6.1 | Lymphoid cell lymphokines

In an investigative study by Paradinas et al.,[63] intralesional lymphoid cell lymphokines (LCL-LK) were injected into cutaneous breast metastases. This study found LCL-LK to be effective in promoting tumor cell necrosis, demonstrating tumor reduction in 7 out of 10 lesions but none demonstrated complete resolution.[63]

5.6.2 | Dendritic cell therapy

Intralesional dendritic cell therapy is another proposed immunotherapy that manipulates the broad antigen-presenting function of dendritic cells.[64] In a pilot study by Triozzi et al.,[64] dendritic cells derived from monocytes and macrophages administered intralesionally into CMBC led to tumor regression in 6 out of 10 patients as early as 4 days after injection. There is currently a clinical trial recruiting to explore the use of vaccination of autologous dendritic cells with onco-peptides with adjuvant cytokines in metastatic breast cancer (https://clinicaltrials.gov/ct2/show/NCT00197925).

5.6.3 | Interferon therapy

Interferons (IFNs) have been evaluated as an intralesional injection for CMBC in one study by Habif et al.[65] In this prospective study, nIFN-α was tested as a monotherapy and in combination with nIFN-γ. In the 12 patients receiving nIFN- α monotherapy, one lesion had complete regression, 11 reduced in size, and 4 remained stable.[65] In the four patients treated with nIFN-α and nIFN-γ combination therapy, all lesions demonstrated partial regression.[65]

5.7 | Electrochemotherapy

ECT is the application of electric pulses to increase the permeability of tumor cells, improving the penetration of hydrophilic chemotherapy drugs. This local outpatient therapy results in increased cytotoxicity of the drug, while minimizing systemic toxicities.[66,67] ECT has been gaining popularity as a palliative treatment for CMBC.[68]

Most commonly, ECT is used to deliver bleomycin, which is injected intratumorally or intravenously, depending on the size of the tumor. Intratumoral injection is used for tumors less than 3 cm^2, while intravenous injection is used for tumors larger than 3 cm^2 or in cases of extensive cutaneous metastases.[17,69–73] It is postulated that for large, fibrotic tumors, cancer cells are more difficult to access via the intratumoral route, resulting in decreased penetration and uneven distribution of the drug.[17,67]

Outcomes for ECT are variable, as represented in 16 studies totaling 440 patients. The complete response rate per total number of lesions ranged from 33%[74] to 75.3%,[2] and the partial response rate ranged from 15%[66] to 67%.[74] Notably, response to treatment occurs as early as 1 week to 1 month after the first treatment, with patients reporting decreased symptoms of pain, exudate, and malodor.[75,76]

5.8 | Targeted therapy

5.8.1 | Bevacizumab

Bevacizumab is an anti-VEGF factor, designed to inhibit neoangiogenesis in tumor cells. It is given as an intravenous infusion, usually every 2–3 weeks. There are two publications reporting the use of Bevacizumab in CMBC.[77] In a case report by Gui et al.,[78] the patient saw a rapid improvement of cutaneous metastases up until the 46-month follow-up period. A retrospective study by Cottu et al.[77] resulted in skin necrosis and expansion of the skin lesions in 9 out of 12 patients. In addition to daily wound care, three of these patients required surgical resection and flap reconstruction following a 4-week bevacizumab washout period to preserve the skin's healing ability.[77] Despite this study's small sample size, it demonstrates the potentially deleterious effects of bevacizumab on wound healing; therefore, further studies are needed to investigate its utility in CMBC.

5.8.2 | Sunitinib

Sunitinib is a receptor tyrosine kinase inhibitor that is taken as a daily oral capsule. A standard treatment regimen consists of 4 weeks of treatment, followed by 2 weeks without treatment. Sunitinib has been studied in two clinical trials in patients with metastatic and locoregionally recurrent breast cancer.[79,80] Tyrosine kinase inhibitors are a large family of receptors that include platelet-derived growth factor receptors, fibroblast growth factor receptors, and vascular endothelial-derived growth factors (VEGFs).[79,80] They have an established role in tumor growth and angiogenesis by disrupting VEGF signaling using antibodies or antagonists.[79] In a Phase II clinical trial by Yardley et al.,[79] a daily 37.5-mg oral dose achieved a combined complete and partial response rate of 20% in the 15 patients presenting with cutaneous lesions. A case report by Puente et al.[80] achieved a partial cutaneous tumor response after two cycles of trastuzumab chemotherapy and a daily dose of oral sunitinib.

5.8.3 | Pembrolizumab

Pembrolizumab is an immunomodulator used in the treatment of TNBC.[81] It is given as an intravenous infusion every 3 or 6 weeks. It is an antibody targeted against the PD-1 ligand (PD-L1), a surface molecule expressed in many solid tumors, that inactivates antitumor

immune responses in T cells.[81] It was described in a case report by one of our coauthors, Yuan et al.,[81] who used pembrolizumab in conjunction with a p53MVA vaccine.[81] The p53MVA vaccine was designed to present p53 as an antigen to trigger antitumor activity by the immune system. The patient in this study had previously failed various chemotherapy regimens.[81] After she received the p53MVA vaccine in conjunction with pembrolizumab, she had complete regression of her cutaneous metastases within 9 weeks. Interestingly, she had continued metastatic control by the end of the study's 33-week follow-up period.[81]

5.8.4 | Intracellular phosphatidylinositol-3-kinase

Intracellular phosphatidylinositol-3-kinase (PI3K) has been studied in a Phase I clinical trial by Blagden et al.[82] for its role in cell regulatory pathways. In this trial, a Class I PI3K inhibitor CH51327799 was prescribed orally to patients with advanced solid tumor cancers. Findings from this study did not achieve an objective response rate, but found one TN breast cancer patient to have improved cutaneous lesions for six cycles.[82]

5.8.5 | CAR-T therapy

Chimeric antigen receptor T-cell (CAR-T) therapy employs genetically engineered T cells to produce artificial T-cell receptors targeted for specific proteins.[83] Tchou et al.[84] investigated the use of c-Met, a hepatocyte growth factor receptor expressed in solid tumors including breast cancer. In this Phase 0 study, genetically modified c-Met CAR T cells were injected intratumorally and were found to be a viable and provide a safe avenue of treatment for CMBC.[84] A Phase I trial for the use of intravenous mRNA c-Met-CAR T cells was recently completed on four metastatic breast cancer and three melanoma patients which resulted in four cases of stable disease and three cases of progressive disease.[85]

5.8.6 | Oncolytic viral therapy

Oncolytic viral therapy is a growing area of interest in breast cancer treatment, with current studies studying its use as a single agent immune-virotherapy, or in combination with existing immunotherapies. Oncolytic viruses are natural or artificially modified viruses that selectively infect and replicate in tumor cells, sparing normal cells, and resulting in tumor lysis.[86] Two broad classes of oncolytic virotherapy exist: nonreplicating and replicating viruses.

Nonreplicating viruses act as vectors that deliver toxic antitumor genes or genes that activate cancer prodrugs given in combination therapy.[87] The most widely studied are 1) the herpes simplex virus (HSV)-thymidine kinase (TK) gene given with prodrug ganciclovir, and the cytosine deaminase gene, given with prodrug 5-flucytosine.[87] Both strategies are currently in human clinical trials.

Replicating oncolytic viruses are engineered to specifically target and replicate within cancer cells. These produce direct cancer-killing through tumor cell lysis and indirectly, by activating the local tumor environment to express more checkpoint targets and recruit effector immune cells.[87] The most widely studied replicating oncolytic viruses for breast cancer are adenovirus, HSV, and vaccinia virus (VACV).[87] Similarly, in a pilot study by Kimata et al., HSV type 1 mutant, HF10, was injected intratumorally into cutaneous metastases in six breast cancer patients.[86] This study found HF10 to have a 30%–100% histologic malignant cell death rate compared to a 0% cell death rate in saline injection controls.[86] A number of other oncolytic viruses are now being tested in humans as treatments for locally recurrent breast cancer.

5.9 | Other novel agents

Other novel agents in the literature include bacterial-derived recombinant antibody toxin scFv(FRP5)-ETA. This agent has specificity for ErbB receptors, which are overexpressed in tumor cells. Azemar et al.,[88] demonstrated intratumoral injection of scFv(FRP5)-ETA to reduce cutaneous tumor size in 6 out of 10 CMBC, colorectal, and melanoma patients.

Topical calcipotriol therapy is another agent that uses vitamin D to inhibit cellular proliferation in vitro.[89] A study by Bower et al.,[89] used topical calcipotriol on 19 patients, and found as high as a 50% reduction in tumor diameter.

6 | DISCUSSION

Currently, there is no clear protocol for treating cutaneous metastases in breast cancer and limited data regarding the role of cutaneous metastasectomy. The presence of concomitant visceral metastases in patients diagnosed with CMBC will determine overall survival, but the incidence of this is unknown. Anecdotally, we have noticed that patients presenting with extensive cutaneous metastases usually do have visceral metastases. At our cancer institute, we are currently establishing a retrospective database, studying all our cutaneous metastases patients from 2010 to present, to ascertain the incidence of concurrent visceral metastases. Without this information, it is hard to determine whether a patient presenting with a limited number of cutaneous metastases represents oligometastases. The concept of oligometastases has been around for over a century, but has recently experienced a revival.[90] Oligometastases is the concept that limited spread of disease represents all the metastatic foci the patient has or will ever develop.[90] This is in contrast with the idea that these lesions represent the early manifestation of what will become widely disseminated disease.[90] Clearly patients with oligometastases would be more suitable candidates for surgical excision.

A major concern for surgical treatment is the potential for rapid recurrence after excision. It has been suggested that rapid recurrence may result from local therapy, leading to the recruitment or activation

of previously quiescent cancer cells.[90] We did not find this to be a common problem in the literature. Positive surgical margins are known to be a predictor for local failure in curative-intent metastasectomy literature.[91] Unlike with primary skin cancers, such as melanoma or squamous cell carcinoma, where there are specific guidelines on margins of excision, the surgical approach to cutaneous metastases is uncommon and arbitrary. These patients may have had previous breast reconstruction or mastectomy with or without reconstruction. There may be a lack of enthusiasm to cause a large chest wall defect that may require complex reconstruction in a patient with recurrent disease. We recently reported a case series describing our experience with a local thoracoabdominal advancement flap, that allows for immediate chest wall coverage after radical mastectomy, from fungating breast cancer.[4] This technique could potentially allow a wider area of resection of cutaneous metastases with minimal morbidity in some cases (Figure 6A–D).

Other considerations for surgical management of CMBC is the limited value in patients with concomitant visceral metastases. Metastasectomy should perhaps be restricted to those with skin and subcutaneous tissue involvement only, since this would have the greatest impact on overall cytoreduction. A retrospective study by Hu et al.[92] found CMBC patients without visceral metastases to have 1-, 3-, 5-, and 10-year cumulative survival rates of 79%, 51%, 37%, and 11%. Given the long-term survival rates in this study, definitive surgical management may be a feasible treatment option for CMBC patients with metastases confined to the skin. Furthermore, for patients maintained on systemic therapy for visceral metastases, these medications are often held before surgery to allow healing, which would lead to worsening of the overall metastatic disease control.

Surgery is a potentially viable method of local control of cutaneous metastases, provided negative margins can be achieved. This means that only cutaneous metastases that occupy a limited area that can be primarily closed or reconstructed with local skin advancement or flaps should be considered. In general, we recommend an elliptical excision where primary closure is possible (Figure 3A) Cutaneous metastases close to a previous mastectomy scar could be resected with wide margins (Figure 6A) and closed using a local thoracoabdominal advancement flap (Figure 6C,D). Split thickness skin grafts can also be considered and is a relatively low morbidity surgery.[30] Where larger extensive areas of skin are involved, we would not recommend surgical resection (Figure 3B–D). As long as the selection of candidates is reasonable, the morbidity of metastasectomy in CMBC should have low morbidity.[92] This is in contrast to metastasectomy in the setting of thoracic or cerebral metastases. If the skin lesions are limited, surgery may achieve such high rates of cytoreduction that disease-free survival is improved.

With regard to nonsurgical modalities, a consensus on which therapies to use has yet to be established due to the paucity of data.

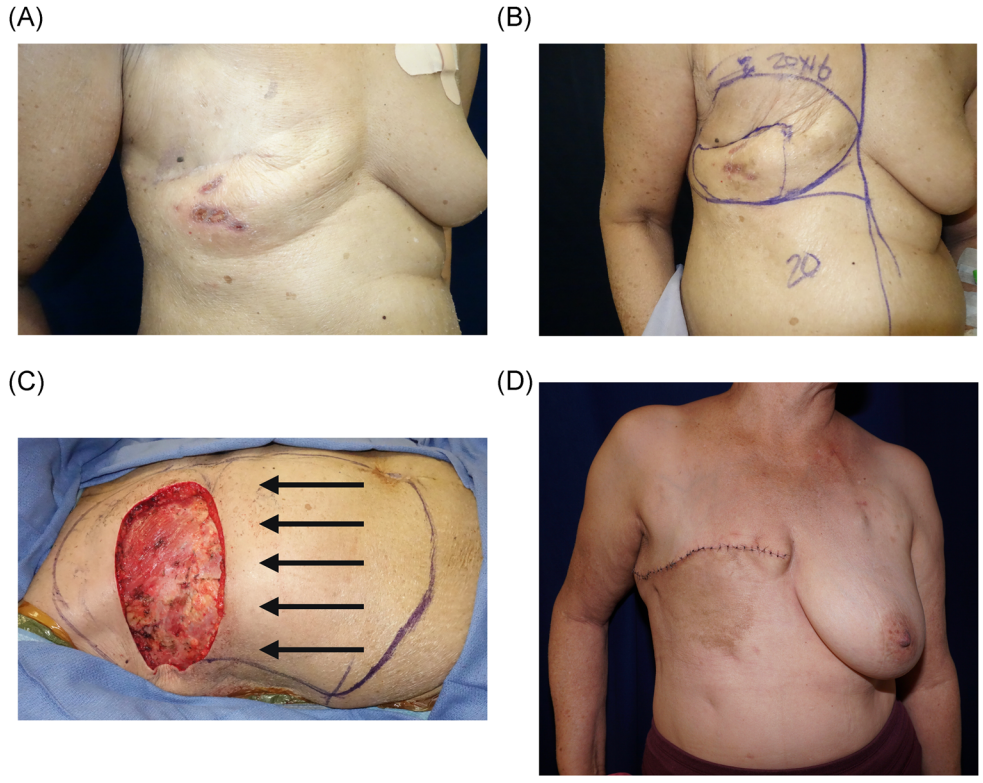

FIGURE 6 (A–D) This 67-year-old female with skin metastases (A) presenting 2 years after right mastectomy (B). She underwent wide local excision and closed with local thoracoabdominal advancement flap (C) followed by chest wall radiation. She is free of local recurrence at 3 years but has since developed contralateral axillary metastases and pulmonary metastases (D)

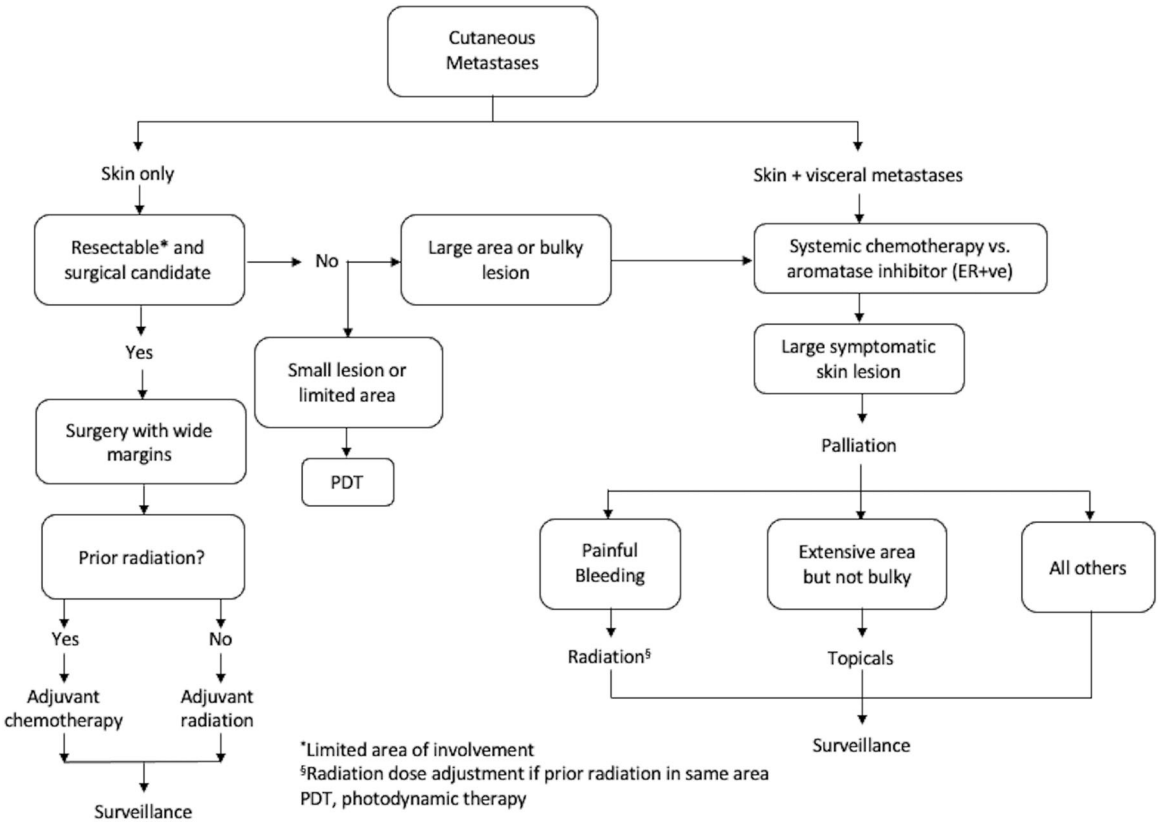

FIGURE 7 Proposed cutaneous metastases treatment algorithm

Most publications involve only a small number of patients and are largely case reports and case series. The general consensus is that management of cutaneous metastases in the setting of any primary cancer should be based on the extent of disease. Patients with visceral metastases tend to have a worse prognosis and should undergo systemic therapy. In breast cancer patients the decision for chemotherapy versus aromatase inhibitors is dependent on tumor phenotype. For HER2 + breast cancer patients, trastuzumab, ado-trastuzumab emtansine, and lapatinib have demonstrated to be effective in reducing cutaneous lesions in several case reports.[51–53] Patients with ER + disease are better suited for aromatase inhibitors, either as the initial treatment or as maintenance therapy following disease control by other systemic and local therapies.[56–60]

Local nonsurgical therapy should be reserved for patients without visceral metastases or in extensive disease requiring symptom palliation. These include patients who have bone or cerebral metastases but also extensive drainage from their cutaneous metastases (Figure 3C). In both cases, the more common approach is multimodal therapy consisting of radiotherapy and chemotherapy. The remaining modalities are rarely available and only a few centers have access. Of them, topical therapies are the next most trialed modalities, used exclusively as adjuvant therapy. The most widely studied is imiquimod, with more recent studies demonstrating the potential for oxygen flow-assisted topical administration of metho-trexate 5% (OFAMTX5%) and topical 5-fluorouracil used in combination with cryotherapy. Less commonly used in clinical practice are photodynamic therapy and ECT. Yet, they are some of the more commonly studied modalities in the literature. While both have demonstrated symptomatic relief in recent case studies, it is not discernable how each is chosen. This may be based on each institutions' access to facilities and clinical expertise, to enable them to perform these procedures. Notably, photodynamic therapy is reserved for smaller, more superficial lesions in the earlier stages of disease progression.[31]

Of the newer and less studied therapies, oncolytic viral therapy, pembrolizumab, and CAR-T cell therapy have all shown the most promise; however, these remain in the "experimental" stages of development. At our institution, we have access to all three of these modalities and it is our hope to publish data in the near future, to establish their effectiveness in this challenging problem.

7 | CONCLUSION

Cutaneous metastases are a relatively common occurrence in patients with breast cancer. There are a range of treatment modalities, with varying levels of effectiveness and there is no data suggesting any one particular method to be superior.

We believe there is a need for well-designed clinical trials comparing treatment protocols that focus on improving quality of life

and long-term survival. In particular, we suggest the role of surgical resection in limited cutaneous metastasis be investigated as an initial management approach, given its potential to both palliate symptoms such as bleeding, drainage, and pain, and potential to cure select patients. We present a potential algorithm with surgical resection as the first-line option (Figure 7). We propose that to proceed with surgery, the following criteria must be fulfilled: 1. Absence of visceral metastases; 2. The involved area should be resectable, with a goal of margin-free resection; (involved margins may be responsible for some reported "rebound" phenomena); 3. The resulting defect should be amenable to primary closure or local options for soft tissue/skin coverage; and 4. The patient must be a surgical candidate and willing to undergo surgical resection. Furthermore, we suggest that surgical. excision should be followed by adjuvant therapy with radiation or chemotherapy.

We are currently trying to design a prospective clinical trial to look at surgical excision of limited cutaneous metastases, for instance, a single nodule. Given the heterogeneity of the presentation of CMBC, such a trial is proving to be a challenge to implement. The ultimate goal is to develop a standard of care that will give these patients the best quality of life and, potentially, improve survival with this challenging condition.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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REFERENCES

1. Moore S. Cutaneous metastatic breast cancer. *Clin J Oncol Nurs*. 2002;6(5):255-260. doi:10.1188/02.CJON.255-260
2. Benevento R, Santoriello A, Perna G, Canonico S. Electrochemotherapy of cutaneous metastastes from breast cancer in elderly patients: a preliminary report. *BMC Surg*. 2012;12(Suppl 1):S6. doi:10.1186/1471-2482-12-S1-S6
3. Chisti MA, Alfadley AA, Banka N, Ezzat A. Cutaneous metastasis from breast carcinoma: a brief report of a rare variant and proposed morphological classification. *Gulf J Oncol*. 2013;1(14):90-94. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84910067414%26partnerID=40%26md5=e5a9e8bcbddbf610bf9e54505eb65fd9
4. Fahradyan A, Liu A, Taylor L, Jones V, Li W-Y. Short Stay Management of locally advanced breast cancer using immediate local thoraco-abdominal advancement flap and ERAS protocol. Ann Plastic Surg. n.d.
5. Chippa V, Barazi H. Inflammatory breast cancer. *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021. http://www.ncbi.nlm.nih.gov/books/NBK564324
6. Yaghoobi R, Talaizade A, Lal K, Ranjbari N, Sohrabiaan N, Feily A. Inflammatory breast carcinoma presenting with two different patterns of cutaneous metastases: carcinoma telangiectaticum and carcinoma erysipeloides. *J Clin Aesthet Dermatol*. 2015;8(8):47-51.
7. Henriques L, Palumbo M, Guay M-P, et al. Imiquimod in the treatment of breast cancer skin metastasis. *J Clin Oncol*. 2014;32(8):e22-e25. doi:10.1200/JCO.2012.46.4883
8. Kong JH, Park YH, Kim JA, et al. Patterns of skin and soft tissue metastases from breast cancer according to subtypes: relationship between EGFR overexpression and skin manifestations. *Oncology*. 2011;81(1):55-62. doi:10.1159/000331417
9. Kong Y, Zhang X, Zhao Y, Xue Y, Zhang Y. Uptake of DNA by cancer cells without a transfection reagent. *Biol Res*. 2017;50(1):2. doi:10.1186/s40659-017-0107-x
10. Araújo E C A, Barbosa M, Costa R, Sousa B, Costa V. A first sign not to be missed: cutaneous metastasis from breast cancer. *Eur J Case Rep Intern Med*. 2020;7(1):14. doi:10.12890/2020_001356
11. Prabhu S, Pai S, Handattu S, Kudur M, Vasanth V. Cutaneous metastases from carcinoma breast: the common and the rare. *Indian J Dermatol Venereol Leprol*. 2009;75(5):499-502. doi:10.4103/0378-6323.55395
12. Allison R, Mang T, Hewson G, Snider W, Dougherty D. Photodynamic therapy for chest wall progression from breast carcinoma is an underutilized treatment modality. *Cancer*. 2001;91(1):1-8. doi:10.1002/1097-0142(20010101)91:1%3C1::AID-CNCR1%3E3.0.CO;2-P
13. Ollila DW. Complete metastasectomy in patients with stage IV metastatic melanoma. *Lancet Oncol*. 2006;7(11):919-924. doi:10.1016/S1470-2045(06)70938-X
14. Strickley JD, Jenson AB, Jung JY. Cutaneous metastasis. *Hematol Oncol Clin North Am*. 2019;33(1):173-197. doi:10.1016/j.hoc.2018.08.008
15. Nelson DW, Fischer TD, Graff-Baker AN, et al. Impact of effective systemic therapy on metastasectomy in stage IV melanoma: a matched-pair analysis. *Ann Surg Oncol*. 2019;26(13):4610-4618. doi:10.1245/s10434-019-07487-5
16. Enomoto LM, Levine EA, Shen P, Votanopoulos KI. Role of surgery for metastatic melanoma. *Surg Clin North Am*. 2020;100(1):127-139. doi:10.1016/j.suc.2019.09.011
17. Bourke MG, Salwa SP, Sadadcharam M, et al. Effective treatment of intractable cutaneous metastases of breast cancer with electrochemotherapy: ten-year audit of single centre experience. *Breast Cancer Res Treat*. 2017;161(2):289-297. doi:10.1007/s10549-016-4046-y
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clin Res Ed)*. 2009;339:b2700. doi:10.1136/bmj.b2700
19. Ackley B, Ladwig G, Swan BA, Tucker S. Evidence based nursing care guidelines. *Medical Surgical Interventions*. Vol 15. Mosby Elsevier; 2008.
20. Varricchio A, Di Libero L, Iannace C. Reconstruction with cutaneous flap after resection for breast cancer's skin metastases in a chemoresistant patient. *Ann Ital Chir*. 2013;84. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84929940611%26partnerID=40%26md5=5378961ddc0f39987d8819c51ed09e03
21. Goto H, Omodaka T, Yanagisawa H, et al. Palliative surgical treatment for cutaneous metastatic tumor is a valid option for improvement of quality of life. *J Dermatol*. 2016;43(1):95-98. doi:10.1111/1346-8138.12983
22. Clive S, Gardiner J, Leonard RCF. Miltefosine as a topical treatment for cutaneous metastases in breast carcinoma. *Cancer Chemother Pharmacol*. 1999;44(Suppl):S29-S30. doi:10.1007/s002800051114

23. O'rourke S, Galea MH, Morgan D, et al. Local recurrence after simple mastectomy. *Br J Surg*. 1994;81(3):386-389. doi:10.1002/bjs.1800810321
24. Muller KE, Zhao L, Jorns JM. Metastatic and hematolymphoid neoplasms involving the breast: 20-year experience at a Tertiary Center. *Breast J*. 2018;24(4):680-682. doi:10.1111/tbj.13020
25. O'Brien R, Porto DA, Friedman BJ, Douglass MC. Elderly female with swelling of the right breast. *Ann Emerg Med*. 2016;67(6):e25-e26. doi:10.1016/j.annemergmed.2015.11.014
26. Gilliland MD, Larson DL, Copeland EM. Appropriate timing for breast reconstruction. *Plast Reconstr Surg*. 1983;72(3):335-337. doi:10.1097/00006534-198309000-00013
27. Santiago F, Saleiro S, Brites MM, Frutuoso C, Figueiredo A. A remarkable case of cutaneous metastatic breast carcinoma. *Dermatol Online J*. 2009;15(7). https://www.scopus.com/inward/record.uri?eid=2-s2.0-69049107708%26partnerID=40%26md5=0b0dfc6f7f52ac9cf420a447fafa7b71
28. Salvadori B, Rovini D, Squicciarini P, Conti R, Cusumano F, Grassi M. Surgery for local recurrences following deficient radical mastectomy for breast cancer: a selected series of 39 cases. *Eur J Surg Oncol*. 1992;18(5):438-441. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0026494543%26partnerID=40%26md5=eac29bf52705be755aa1dde877b74855
29. Alizadeh N, Mirpour H, Azimi SZ. Scalp metastasis from occult primary breast carcinoma: a case report and review of the literature. *Int J Women's Dermatol*. 2018;4(4):230-235. doi:10.1016/j.ijwd.2018.08.002
30. Lam C, Wilkinson M, Billingsley E. Mohs micrographic surgery for cutaneous metastasis of breast cancer. *Dermatol Surg*. 2013;39(10):1537-1539. doi:10.1111/dsu.12274
31. Zeitouni NC, Shieh S, Oseroff AR. Laser and photodynamic therapy in the management of cutaneous malignancies. *Clin Dermatol*. 2001;19(3):328-338. doi:10.1016/S0738-081X(01)00170-5
32. Rollakanti KR, Anand S, Maytin EV. Vitamin D enhances the efficacy of photodynamic therapy in a murine model of breast cancer. *Cancer Med*. 2015;4(5):633-642. doi:10.1002/cam4.361
33. Lowdell CP, Ash DV, Driver I, Brown SB. Interstitial photodynamic therapy. Clinical experience with diffusing fibres in the treatment of cutaneous and subcutaneous tumours. *Br J Cancer*. 1993;67(6):1398-1403.
34. Allison RR. Photodynamic therapy: oncologic horizons. *Future Oncol*. 2014;10(1):123-142. doi:10.2217/fon.13.176
35. Morrison SA, Hill SL, Rogers GS, Graham RA. Efficacy and safety of continuous low-irradiance photodynamic therapy in the treatment of chest wall progression of breast cancer. *J Surg Res*. 2014;192(2):235-241. doi:10.1016/j.jss.2014.06.030
36. Mang TS, Allison R, Hewson G, Snider W, Moskowitz R. A phase II/III clinical study of tin ethyl etiopurpurin (Purlytin)-induced photodynamic therapy for the treatment of recurrent cutaneous metastatic breast cancer. *Cancer J*. 1998;4(6):378-384. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031793840%26partnerID=40%26md5=6a564548dcaba7e286e8facb4989d473
37. Lapes M, Petera J, Jirsa M. Photodynamic therapy of cutaneous metastases of breast cancer after local application of meso-tetra-(para-sulphophenyl)-porphin (TPPS4). *J Photochem Photobiol B*. 1996;36(2):205-207.
38. Bubna AK. Imiquimod – its role in the treatment of cutaneous malignancies. *Indian J Pharmacol*. 2015;47(4):354-359. doi:10.4103/0253-7613.161249
39. Henriques L, Palumbo M, Guay M-P, et al. Imiquimod in the treatment of breast cancer skin metastasis. *J Clin Oncol*. 2014;32(8):e22-e25. doi:10.1200/JCO.2012.46.4883
40. Dewan MZ, Vanpouille-Box C, Kawashima N, et al. Synergy of topical toll-like receptor 7 agonist with radiation and low-dose cyclophosphamide in a mouse model of cutaneous breast cancer. *Clin Cancer Res*. 2012;18(24):6668-6678. doi:10.1158/1078-0432.CCR-12-0984
41. Salazar LG, Lu H, Reichow JL, et al. Topical imiquimod plus nab-paclitaxel for breast cancer cutaneous metastases: a phase 2 clinical trial. *JAMA Oncol*. 2017;3(7):969-973. doi:10.1001/jamaoncol.2016.6007
42. Jouret G, Gonne E, Quatresooz P, et al. Cutaneous breast cancer metastases successfully treated using an oxygen flow assisted topical administration of methotrexate (OFAMTX). *Dermatol Ther*. 2020;10(4):855-861. doi:10.1007/s13555-020-00393-9
43. Krishnasamy SR, Almazan TH, Suero-Abreu GA, Jung JY. Successful treatment of cutaneous metastatic breast cancer with topical treatments that potentially synergize with systemic therapy: a case series. *JAAD Case Rep*. 2018;4(7):711-715. doi:10.1016/j.jdcr.2018.04.013
44. Terwogt JMM, Mandjes IAM, Sindermann H, Beijnen JH, Ten Bokkel Huinink WW. Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast cancer. *Br J Cancer*. 1999;79(7-8):1158-1161. doi:10.1038/sj.bjc.6690184
45. Leonard R, Hardy J, van Tienhoven G, et al. Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol*. 2001;19(21):4150-4159.
46. Jatoi A, Suman VJ, Schaefer P, et al. A phase II study of topical ceramides for cutaneous breast cancer. *Breast Cancer Res Treat*. 2003;80(1):99-104. doi:10.1023/A:1024409123726
47. Fritz P, Hensley FW, Berns C, Harms W, Wannenmacher M. Long-term results of pulsed irradiation of skin metastases from breast cancer. Effectiveness and sequelae. *Strahlenther Onkol*. 2000;176(8):368-376.
48. Raszewski ŁJ, Chyrek A, Marciniak M, Burchardt W, Bielęda GM, Chicheł A. High-dose-rate surface brachytherapy as a treatment option for renal cell carcinoma cutaneous metastases. *J Contemp Brachytherapy*. 2021;13(3):331-337. doi:10.5114/jcb.2021.105947
49. Poovaneswaran S, Lee ZEJ, Lim WY, Raja Gopal NS, Dali FM, Mohamad I. Cutaneous lesions as a presenting sign of metastases in male breast cancer: a rare clinical entity. *Med J Malaysia*. 2013;68(2):168-170. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84876905197%26partnerID=40%26md5=b4d2aacf84d1461f2bd15506edda33ce
50. La Verde N, Moretti A, Farina G, et al. Eribulin in cutaneous breast cancer metastasis treatment: clinical activity and symptom control. *Future Oncol*. 2013;9(12):1841-1848. doi:10.2217/fon.13.216
51. Giarratano T, Miglietta F, Giorgi CA, et al. Exceptional and durable responses to TDM-1 after trastuzumab failure for breast cancer skin metastases: potential implications of an immunological sanctuary. *Front Oncol*. 2018;8:581. doi:10.3389/fonc.2018.00581
52. Kamaraju S, Depke J, Povletich J, Currey A, Weil E. Cutaneous metastasis due to breast cancer in a patient with primary biliary cirrhosis: a case report. *Case Rep Oncol*. 2016;9(3):718-725. doi:10.1159/000452145
53. Noguchi E, Kamio T, Kamio H, et al. Efficacy of lapatinib monotherapy on occult breast cancer presenting with cutaneous metastases: a case report. *Oncol Lett*. 2014;8(6):2448-2452. doi:10.3892/ol.2014.2594
54. Pizzuti L, Sergi D, Barba M, Vici P. Unusual long-lasting cutaneous complete response to lapatinib and capecitabine in a heavily pretreated HER2-positive plurimetastatic breast cancer patient. *Tumori*. 2013;99(3):e127-e130. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84886056753%26partnerID=40%26md5=b04f94305a41606a044048dc5e8969e8
55. Franchina T, Adamo B, Ricciardi GRR, et al. Activity of pegylated liposomal doxorubicin in combination with gemcitabine in triple negative breast cancer with skin involvement: two case reports. *Cancer Biol Ther*. 2012;13(7):472-476. doi:10.4161/cbt.19593

56. Sedloev T, Vlahova A, Usheva S, Vasileva-Slaveva M, Spiridonova T, Spirdonov J. Long-term survival and complete response to anastrozole in breast cancer patient with cutaneous metastases only. *Anticancer Res*. 2019;39(8):4393-4398. doi:10.21873/anticanres.13609
57. Micallef RA, Boffa MJ, Degaetano J, Muscat V. Melanoma-like pigmented cutaneous metastases from breast carcinoma. *Clin Exp Dermatol*. 2004;29(2):144-146. doi:10.1111/j.1365-2230.2004.01458.x
58. Richtig E, Gerger A, El-Shabrawi-Caelen L, Szkandera J, Hofmann-Wellenhof R. Reflectance confocal microscopy in early diagnosis of cutaneous metastases of breast cancer. *Gynecol Oncol*. 2009;115(3):510-511. doi:10.1016/j.ygyno.2009.08.030
59. Dave SR, Samuel TA, Pucar D, Savage N, Williams HT. FDG PET/CT in evaluation of unusual cutaneous manifestations of breast cancer. *Clin Nucl Med*. 2015;40(1):e63-e67. doi:10.1097/RLU.0000000000000553
60. del Puerto Troncoso C, Muñoz-Leiva D, Jaque-Silva A, González Bombardiere S. Breast cancer metastasis misdiagnosed as an angiokeratomatous eruption. an infrequent presentation. Case report. *Am J Dermatopathol*. 2016;38(4):302-304. doi:10.1097/DAD.0000000000000487
61. Damaskos C, Dimitroulis D, Pergialiotis V, et al. An unexpected metastasis of breast cancer mimicking wheal rush. *G Chir*. 2016;37(3):136-138. doi:10.11138/gchir/2016.37.3.136
62. Özet A, Yilmaz MI, Yavuz AA, Ozturk B, Komurcu S, Arpaci F. A 10-year delayed breast cancer patient with unusual widespread cutaneous involvement and visceral metastases. *Breast Journal*. 2003;9(1):54-55. doi:10.1046/j.1524-4741.2003.09110.x
63. Paradinas FJ, Southcorr BM, O'Connell D, et al. Changes induced by local injection of human lymphoid cell lymphokine into dermal metastases of breast carcinoma: a light and electron microscopical study. *J Pathol*. 1982;138(4):309-323. doi:10.1002/path.1711380403
64. Triozzi PL, Khurram R, Aldrich WA, Walker MJ, Kim JA, Jaynes S. Intratumoral injection of dendritic cells derived in vitro in patients with metastatic cancer. *Cancer*. 2000;89(12):2646-2654. doi:10.1002/1097-0142(20001215)89:12%3C2646::AID-CNCR18%3E3.0.CO;2-A
65. Habif DV, Ozzello L, De Rosa CM, Cantell K, Lattes R. Regression of skin recurrences of breast carcinomas treated with intralesional injections of natural interferons alpha and gamma. *Cancer Invest*. 1995;13(2):165-172. doi:10.3109/07357909509011686
66. Falk H, Matthiessen LW, Wooler G, Gehl J. Calcium electroporation for treatment of cutaneous metastases; a randomized double-blinded phase II study, comparing the effect of calcium electroporation with electrochemotherapy. *Acta Oncol*. 2018;57(3):311-319. doi:10.1080/0284186X.2017.1355109
67. Testori A, Tosti G, Martinoli C, et al. Electrochemotherapy for cutaneous and subcutaneous tumor lesions: a novel therapeutic approach. *Dermatol Ther*. 2010;23(6):651-661. doi:10.1111/j.1529-8019.2010.01370.x
68. Kendler M, Micheluzzi M, Wetzig T, Simon JC. Electrochemotherapy under tumescent local anesthesia for the treatment of cutaneous metastases. *Dermatol Surg*. 2013;39(7):1023-1032. doi:10.1111/dsu.12190
69. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. *Ann Intern Med*. 1990;113(9):656-663. doi:10.7326/0003-4819-113-9-656
70. Kreuter A, van Eijk T, Lehmann P, et al. Electrochemotherapy in advanced skin tumors and cutaneous metastases – a retrospective multicenter analysis. *J Germ Soc Dermatol*. 2015;13(4):308-315. doi:10.1111/ddg.12583
71. Morley J, Grocott P, Purssell E, Murrells T. Electrochemotherapy for the palliative management of cutaneous metastases: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2019;45(12):2257-2267. doi:10.1016/j.ejso.2019.07.003
72. Matthiessen LW, Keshtgar M, Curatolo P, et al. Electrochemotherapy for breast cancer—results from the INSPECT database. *Clin Breast Cancer*. 2018;18(5):e909-e917. doi:10.1016/j.clbc.2018.03.007
73. Skarlatos I, Kyrgias G, Mosa E, et al. Electrochemotherapy in cancer patients: first clinical trial in Greece. *In Vivo*. 2011;25(2):265-274. https://www.scopus.com/inward/record.uri?eid=2-s2.0-79955000188%26partnerID=40%26md5=fb948e715e670bd497d95d331048424d
74. Rebersek M, Cufer T, Cemazar M, Kranjc S, Sersa G. Electrochemotherapy with cisplatin of cutaneous tumor lesions in breast cancer. *Anti-Cancer Drugs*. 2004;15(6):593-597. doi:10.1097/01.cad.0000132234.30674.df
75. Solari N, Spagnolo F, Ponte E, et al. Electrochemotherapy for the management of cutaneous and subcutaneous metastasis: a series of 39 patients treated with palliative intent. *J Surg Oncol*. 2014;109(3):270-274. doi:10.1002/jso.23481
76. Campana LG, Galuppo S, Marconato R, Matthiessen LW. Electrochemotherapy for breast cancer. *Handbook of Electroporation*. Vol 3, 2017:2075-2093. doi:10.1007/978-3-319-32886-7_126
77. Cottu PH, Fourchotte V, Vincent-Salomon A, Kriegel I, Fromantin I. Necrosis in breast cancer patients with skin metastases receiving bevacizumab-based therapy. *J Wound Care*. 2011;20(9):403-passim.
78. Gui X, Li H, Song G, Shao B, Jiang H. Long term use of bevacizumab in the treatment of triple negative breast cancer with giant tumor in chest wall. *Medicine*. 2018;97(48):13410. doi:10.1097/MD.0000000000013410
79. Yardley DA, Dees EC, Myers SD, et al. Phase II open-label study of sunitinib in patients with advanced breast cancer. *Breast Cancer Res Treat*. 2012;136(3):759-767. doi:10.1007/s10549-012-2285-0
80. Puente J, Manzano A, Martin M, López-Tarruella S, Díaz-Rubio E. Breast cancer: complete response with the combination of sunitinib and trastuzumab in a patient with grade III ductal carcinoma. *Anti-Cancer Drugs*. 2010;21(Suppl 1):S19-S22. doi:10.1097/01.cad.0000361532.36428.42
81. Yuan Y, Kos FJ, He T-F, et al. Complete regression of cutaneous metastases with systemic immune response in a patient with triple negative breast cancer receiving p53MVA vaccine with pembrolizumab. *Oncoimmunology*. 2017;6(12):e1363138. doi:10.1080/2162402X.2017.1363138
82. Blagden S, Omlin A, Josephs D, et al. First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer. *Clin Cancer Res*. 2014;20(23):5908-5917. doi:10.1158/1078-0432.CCR-14-1315
83. Jensen TI, Axelgaard E, Bak RO. Therapeutic gene editing in haematological disorders with CRISPR/Cas9. *Br J Haematol*. 2019;185(5):821-835. doi:10.1111/bjh.15851
84. Tchou J, Zhao Y, Levine BL, et al. Safety and efficacy of intratumoral injections of chimeric antigen receptor (CAR) T cells in metastatic breast cancer. *Cancer Immunol Res*. 2017;5(12):1152-1161. doi:10.1158/2326-6066.CIR-17-0189
85. Shah PD, Huang ACC, Xu X, et al. Phase I trial of autologous cMET-directed CAR-t cells administered intravenously in patients with melanoma & breast carcinoma. *J Clin Oncol*. 2020;38(15_suppl):10035. doi:10.1200/JCO.2020.38.15_suppl.10035
86. Kimata H, Imai T, Kikumori T, et al. Pilot study of oncolytic viral therapy using mutant herpes simplex virus (HF10) against recurrent metastatic breast cancer. *Ann Surg Oncol*. 2006;13(8):1078-1084. doi:10.1245/ASO.2006.08.035

87. Chaurasiya S, Fong Y. Viroimmunotherapy for breast cancer: promises, problems and future directions. *Cancer Gene Ther*. 2021; 28(7-8):757-768. doi:10.1038/s41417-020-00265-6
88. Azemar M, Djahansouzi S, Jäger E, et al. Regression of cutaneous tumor lesions in patients intratumorally injected with a recombinant single-chain antibody-toxin targeted to ErbB2/HER2. *Breast Cancer Res Treat*. 2003;82(3):155-164. doi:10.1023/B:BREA.0000004371.48757.19
89. Bower M, Stein RC, Hedley A, et al. Topical calcipotriol treatment in advanced breast cancer. *Lancet*. 1991;337(8743):701-702. doi:10.1016/0140-6736(91)90280-3
90. Boffa DJ. Surgeon's perspective to local therapy in oligometastatic cancer. *Cancer J*. 2020;26(2):149-155. doi:10.1097/PPO.0000000000000441
91. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg*. 1997;113(1):37-49. doi:10.1016/s0022-5223(97)70397-0
92. Hu SC-S, Chen G-S, Lu Y-W, Wu C-S, Lan C-CE. Cutaneous metastases from different internal malignancies: a clinical and prognostic appraisal. *J Eur Acad Dermatol Venereol*. 2008;22(6): 735-740. doi:10.1111/j.1468-3083.2008.02590.x

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